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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,658	ZONANA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/16/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,22-26,41,42,59-63,65-69 and 72-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,22-26,41,42, 59-63, 65-69 and 72-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 6/16/05 and a Declaration filed 6/16/05. Claims 5-21, 27-40 and 43-58, 64, 70 and 71 have been cancelled. Claims 72-77 have been added. Claims 1-4, 22-26, 41, 42, 59-63, 65-69 and 72-77 are pending in the application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/16/05 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 2/4/05 and restated below.**

The limitation that the method of increasing hair follicle development, tooth development or sweat gland development comprises administration of an EDA1-II that is the C-terminal 211

amino acids is EDA1-II has been added by submission of claim 69 in the amendment filed 11/22/04. Applicants have indicated that support for this limitation is found on page 21, lines 14-16 and 21-22 and page 22 lines 12-15 and figure 4. These sections teach that within the C-terminal 211 amino acids, a single conservative substitution between Tabby proteins and EDA1-II can be found. These passages and the remainder of the specification do not disclose that the method of increasing EDA1-II can be or should be performed using EDA1-II comprising the C-terminal 211 amino acids. As well, the passages teach generically that a variety of EDA1-II and dL proteins as well as fragments or variants can have therapeutic applications. However, the passages do not teach that a C-terminal 211 amino acid fragment of EDA1-II is one of these fragments of variants that can be used in the recited methods. Therefore, the examiner has been unable to find literal support in the originally filed specification for a method of administering an amount of EDA1-II that is the C-terminal 211 amino acids to promote either hair follicle development, tooth development or sweat gland development. Therefore, the limitation of adding "administration of an EDA1-II that is the C-terminal 211 amino acids" is impermissible NEW MATTER.

Response to Argument

Applicants traverse the claim rejection under 35 U.S.C. 112, first paragraph on pages 5-6 of the amendment filed 6/16/05. Applicants argue that even if there is no literal support for a method of administering an amount of EDA1-II that is the C-terminal 211 amino acids of this protein to a tissue sufficient to promote hair follicle, tooth or sweat gland development, this does not render the language new matter. Applicants point to the MPEP that teaches that the same

words are not required. For support, applicants point to parts of the specification that teach that variants and fragments have therapeutic application.

Applicants' arguments filed 6/16/05 have been fully considered but they are not persuasive. The rejection is not based upon the lack of use of the same words but based upon a lack of support in the specification for use of a fragment comprising the C-terminal 211 amino acids. The specification teaches that a variety of EDA1-II and dL proteins as well as fragments or variants can have therapeutic applications (page 50, line 4-5). Towards, the specifically recited therapeutic application, methods of increasing EDA1-II activity by administration of EDA1-II protein in order to increase hair follicle, tooth and sweat gland development, several proteins are expressly taught. Despite this, the administration of the C-terminal 211 amino acids is not taught. Applicants would like to argue that by describing a variety of fragments and variants, that any of these peptides are inherently intended for the recited method. However, in reference to the C-terminal 211 amino acids, the specification only teaches that this fragment comprises an active domain. The disclosure has not directed use of C-terminal 211 of EDA1-II in a method of increasing hair follicle, tooth and sweat gland development simply by mention of this fragment. Therefore, as regards use of this fragment in the recited method, C-terminal 211 amino acids of EDA1-II is an unnamed species and the specification does not support inclusion of this species in the recited invention.

Claims 1-4, 22-26, 41-42, 59-69 and 72-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing hair follicle or sweat gland development in Tabby mice using an EDA1-II fragment comprising amino acids 239-391,

does not reasonably provide enablement for an increase of hair follicle, sweat gland or tooth development in humans using any EDA1-II fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 5/19/04 and 2/4/05 and restated below. The rejection has been extended to newly added claims 72-77.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method of increasing hair follicle, tooth or sweat gland development by increasing EDA1-II activity.

2) **Scope of the invention**. The claims recite that EDA1-II protein activity can be increased by administration of EDA1-II protein to humans suffering from ectodermal disease. Therefore the instant invention uses methods of protein therapeutics.

3) **Number of working examples and guidance**. Applicants teach that X-linked hypohidrotic ectodermal dysplasia (HED) is a human genetic disorder characterized by lack of hair, sweat glands and tooth development. The EDA1 gene was identified in adult sweat glands. Tabby mice carry a mutant Tabby gene (Ta) and are characterized by an absence of sweat glands

and with anhidrosis and have abnormally shaped teeth. The instant invention is drawn to the identification of an EDA1 splice form EDA1-II that is 94% homologous to the Ta cDNA. Nearly all of the mutations associated with HED are located in the exons coding for this isoform. Based upon this, applicants have proposed assays that are designed to identify agents that enhance EDA1-II activity (page 7, line 32- page 8, line 22). These include *in vivo* methods that involve intradermal injection or topical application of the protein to the skin or tails of newborn tabby mice and detection of the induction of hair growth and injection of proteins into footpads of newborn tabby mice and monitoring of sweat gland development. *In vitro* assays include application of protein to dissected skin from mouse embryos and calculation of hair follicles that follow as well as application of truncated protein to an *in vitro* tooth organ culture system.

Once proteins that enhance EDA1-II activity have been identified, it is taught that the protein can be used in therapeutic applications. Specifically, it is disclosed that purified protein at concentrations ranging from 1 ng/ml to 1 g/ml (a range of 1,000,000) is applied to the tails, bellies and areas behind the ears of newborn tabby mice, wild type mice and nude mice (see page 50, line 21-37) or is injected into footpads of newborn tabby mice (page 51, line 13-24). These methods are said to be extrapolated to humans as well as to application of the protein to *in vitro* tooth cultures and the teeth introduced into humans or other organism (see page 51, line 1-12).

While the specification does not provide an actual reduction to practice of these disclosed methods, post filing results are provided which demonstrate intraperitoneal administration of 10-20 μg of purified 239-391 fragment of human EDA to newborn tabby mice.

4) **State of Art**. The state of art for treatment of humans suffering from ectodermal dysplasia is not currently a high art. Cosmetic or functional correction is the only recourse

patients have against this disease (see e.g. MedlinePlus medical encyclopedia). However, methods based on protein therapeutics for treatment of ectodermal dysplasia is a high art.

Torchilin and Lukyanov teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

Recently, permanent correction of ectodermal dysplasia in tabby mice has been reported (see Gaide and Schneider). In this study, application of EDA1 was conducted in pregnant tabby mice by serial intravenous injections of 400 μg of recombinant EDA1 (in 2mg/ml PBS) following two different dose schedules. Newborn mice received a single intradermal injection at the same dose (see Gaide and Schneider, bridging paragraph page 617-618). Formation of hair, teeth and sweat glands were induced in the newborn mice.

5) **Unpredictability of the art**. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies.

Furthermore, any successes in the published document by Gaide and Schneider cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the reference. Considered in closer detail, the teachings of the instant invention differ dramatically from that of Gaide and Schneider. Gaide and Schneider teach administration of recombinant EDA1-II and the Fc domain of IgG1 that is intravenously injected into pregnant Tabby mice intraperitoneally or intravenously into newborn mice for the sole purpose of altering the phenotype of the fetal mice. None of the treatments were successful in altering any of the Tabby phenotypes in the adult mice. Injections at gestational day 11, 13 and 15 at 400 um per injection, called E11 reversed most of the Tabby characteristics except teeth and hair growth were not completely wild type. Other treatments included gestational treatment at day 15 and 17 (E15) as well as injection of newborn mice at day 2, 3, 5, 9 (D2, D3, D5, D9). The subsequent treatments had decreasing effects on the Tabby phenotype. Newborn injections only consistently corrected sweat gland development. However, teeth and hair were either not or were poorly corrected (see e.g. table 1). Applicants have not proposed injection of pregnant Tabby mice with a recombinant EDA1-II that has been engineered to pass the placental barrier. Furthermore, applicants have not indicated that the EDA1-II would be used to reverse phenotype via genetic routes. Rather the instant specification has indicated that the effects of EDA1-II would be demonstrated in the actual patient injected. Following this approach, the success of treatment in increasing hair follicle, tooth and sweat gland development would be expected to be insufficient in treating each of these disorders as demonstrated by the increasing failure of treatments to reverse the ectodermal phenotype in the newborn mice s demonstrated by Gaide and Schneider.

Therefore, means of administration of protein for the treatment of each of these disorders using the guidance provided in the specification is highly unpredictable.

Problems with protein therapeutics identified in the art are not addressed by the methods of the instant invention nor the prior art. Therefore, neither the specification nor art teach one how to treat ectodermal dysplasia by introduction of EDA1-II as neither the specification nor the prior art provide dosages of EDA1-II to administer to patients, schedule of treatments, specific modes of administration of EDA1-II to humans suffering from ectodermal disease is provided.

6) **Summary**. The invention recites a method of treating ectodermal disease by the administration of EDA1-II protein to a subject using gene therapy. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 6-7 of the amendment filed 4/18/05. Applicant argues the following. 1) As demonstrated by the Declaration 132 (discussed below), a person of skill in the art using the

specification coupled with information known in the art could perform the instantly recited methods. Specifically, applicants argue that the Declaration provides evidence that intraperitoneal administration of 10-20 μg of amino acids 239-391 to newborn Tabby mice induces formation of hair follicles on the tail and formation of sweat glands. The methods used to obtain this data is said to be correlative with the disclosure as the disclosure teaches that amino acids 239-391 can be used to increase hair follicle development and sweat gland development (pages 16, line 29-page 17, line 2, pages 21, lines 21-25, pages 50, lines 21-24, page 51, lines 13-16, page 72, line 22 and 32). 2) Applicants argue that the Tabby mouse is the accepted mouse model for human ectodermal dysplasia and thus provides guidance for use in humans. 3) Applicants argue that the MPEP teaches that data from *in vitro* or animal testing generally supports therapeutic utility.

In the Declaration under 37 CFR 1.132 filed 4/18/05, Dr. Schnieder teaches that Tabby mice are the accepted model of human ectodermal dysplasia as Tabby mice share symptoms with human patients and because X-linked hypohidrotic ectodermal dysplasia and Tabby phenotypes are caused by mutations of the synthetic Ectodysplasia A (Eda) gene on chromosome X. Dr. Schnieder teaches that intraperitoneal administration of 10-20 mg of purified 239-391 fragment of human EDA to newborn tabby mice induces formation of hair on the tail (Exhibit B). The fragment was produced in Cho cells using a PCR3 expression vector comprising the coding sequences for 239-391 of EDA1-II fused to the coding sequence for HA tag. The fragment was secreted into the supernatant and immunoprecipitated. The purified fragment was injected into newborn Tabby mice at day 1 following birth and as demonstrated in figure 1 (exhibit B), hair was detected on the tail of the animals. In a supplemental Declaration filed 6/18/05, Dr.

Schnieder adds that in Figure 3 (Exhibit C), the EDA1-II fragment displayed numerous hairs on the tail as detected in Exhibit B. Simultaneously, sweat gland development was assayed. The results were portrayed in figure 4, which is said to demonstrate that sweat glands were induced by EDA1-II protein fragment. Based upon these results depicted in Exhibit B and C, the applicants argue that the method demonstrates that EDA1-II can induce formation of sweat glands in EDA deficient animals. Thus, applicants conclude that the method can be used to treat ectodermal disorders such as X-linked hypohidrotic ectodermal dysplasia.

Applicants' arguments made 4/19/05 and 6/18/05 have been considered but are not persuasive for the following reason. First, the results in the Declarations have demonstrated that in newborn Tabby mice, a protein fragment of EDA1-II that comprises amino acids 239-391 is able to induce hair formation and sweat gland development. However, applicants' claims are drawn to the ability to induce hair follicle, sweat gland or tooth development or any subset of these in any tissue such as from humans using any EDA1-II protein. It would require undue experimentation to determine what tissues, and what proteins are active in humans to induce hair follicle, sweat gland or tooth development as only a single species of proteins has been identified that is capable of mediating hair follicle and sweat gland development in Tabby mice. Secondly, the methods steps used to produce the results in the Declarations cannot be extrapolated back to the instant specification, as the specification does not provide the correlative teachings. Any difference between the methods provided in the specification and the Declaration can be considered inventive in nature. Furthermore, it is unclear that this process has occurred through an increase in EDA1-II activity, which is specifically recited in multiple claims.

To this end, applicants argue that the Tabby mouse is a model for human ectodermal diseases which disease is specifically recited in claim 42. The art teaches that Ectodermal dysplasia is a clinically heterogenous condition with more than 170 phenotypes and multiple forms. The HED form of Ectodermal dysplasia alone is associated with four genes and three modes of inheritance (Smahi et al page 2372, col 2, paragraph 3). Furthermore, complex signaling is involved in morphogenesis of any of the recited conditions such as hair follicle development. Headon and Overbeck teach that Eda and EdaR are required for primary follicle induction with alternative pathways being responsible for secondary hair follicles. As such Tabby mice actually generate a subset of hair follicles and are only deficient in primary hair follicles (see e.g. page 373, col 1, paragraph 2). Therefore, applicants have presented a mouse, which is specifically deficient in the EDA homologous gene and by replacement demonstrated that hair follicles in newborn mice can be stimulated, which would correspond to the primary hair follicle development but could not overcome defects associated with these alternate pathways. EDA is a clinically complex disorders with multiple phenotypic and genetic characteristics for which the Tabby does not represent a complete model of the disease. The mouse model for analysis of ED taught by Smahi et al teach (2002) is a *NEMO* mouse. NEMO-deficient mice lack an NFkB essential modulator (NEMO), which modulates NFκB and present EDA characteristics. The teachings of Smahi et al implicate NFκB in occurrence of the phenotype of EDA. "Unraveling the molecular bases (sic) of other forms of EDA not associated with mutations in NEMO will possibly implicate other components of the NFκB signaling pathway". Therefore, rescue of EDA by EDA1-II may not overcome complications associated with NFκB, which is supported by Drogmuller et al that teaches that affirms the role of NFκB in

EDA phenotypes (see e.g. page S139, paragraph 1). Treatment of EDA defects then would not be effective to treat EDA associated with NFκB signaling defects.

Finally, applicants argue that in vitro or animal testing supports therapeutic utility. However, the rejection is not based upon a lack of utility but a lack of enablement, which is a distinct rejection from utility. The instant rejection has not been rejected based upon a lack of utility but rather that a method of treatment of ectodermal disease in humans is not enabled based upon the instant specification even in light of what was known in the art at the time of filing. Protein therapy is a highly unpredictable art that to date has had no demonstrable success. Furthermore, as argued above, the models of Tabby mice for the treatment of ectodermal dysplasia is also a high art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 22 and 24-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Matthews et al (US 6,159,462; see entire document) as evidenced by Durmowicz et al (Gene, 2002, Vol 285, pages 203-211; see entire document). **This is a new rejection.**

Matthews et al teach a method of introducing a Wnt polypeptide into a subject. The Wnt polypeptide meets the limitations of the claims as it comprises at least one amino acid that is

100% identical to EDA1-II such as methionine. Durmowicz et al teach that Wnt upregulates expression of EDA (see abstract) and aberrant Wnt signaling leads to EDA-like features (see e.g. page 208, col 2, paragraphs 4-5). Therefore, administration of Wnt would be expected to increase levels of EDA1-II thus leading to hair follicle growth.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

July 11, 2005

JAMES KETTER
PRIMARY EXAMINER